
Correspondence

Need for randomized clinical trials testing targeted therapies in malignant pleural mesothelioma

Dear Sir/s,

In regard to the article “Targeting BAP1: a new paradigm for mesothelioma” by Laurel M. Schunselaar et al., which appeared in *Lung Cancer* (2017); 109: 145–146, discussing BAP1 pathway as a promising therapeutic target for treating mesotheliomas, we would like to discuss the need for randomized clinical trials evaluating the targeted therapies in this disease.

Malignant Pleural Mesothelioma (MPM) is a rare and aggressive tumour affecting the internal lining of the pleura. It is characterized by a poor prognosis and patients normally do not live longer than 12 months [1]. The main cause of this disease is known to be asbestos, although there are some studies pointing at the involvement of Simian virus 40 in its pathogenesis [2–4]. Other factors that may be involved in the pathogenesis include environmental exposure to erionite, fluoro-edenite and ionizing radiation as well as exposure to ceramic fibres [1,5]. The current standard treatment is the combination of cisplatin with pemetrexed [6,7]. However the average survival for this tumour still remains around 1 year. Hence there is an urgent need for a better understanding of the underlying biology of the disease to identify new actionable targets and improve patients’ outcomes. In fact, no targeted therapies have been approved so far for the treatment of the disease. Using data collected from the literature on the very few randomized MPM clinical trials available, we performed a meta-analysis with the aim of investigating the efficacy of targeted therapies in MPM.

The studies were identified according to the following inclusion criteria: 1) participants with advanced MPM; 2) novel targeted agents as the experimental drug; 3) the presence of a control arm for comparison 4) a primary outcome of OS expressed as the hazard ratio (HR) and secondary outcomes of progression-free survival (PFS) expressed as HR. The following exclusion criteria were used: 1) insufficient data were available to estimate the outcomes; 2) animal studies; 3) size of each arm less than 10 participants; 4) non-randomized studies and 5) studies without molecular agents. The summary estimates were generated using a fixed-effect model (Mantel–Haenszel method) [8] or a random-effect model (DerSimonian–Laird-method) [9] depending on the absence or presence of heterogeneity (I^2).

The search yielded 253 potentially relevant articles; 172 studies were excluded, as they were duplicates. After viewing the titles and abstracts of the 81 remaining studies, the full texts of 19 studies were retrieved. Sixteen studies were excluded because they were not Randomized-to controls (RTCs). Finally, 3 studies [10–12] were included in the analysis (Table 1).

A total of 1330 MPM cases were randomly assigned to receive either designated controls or one of three experimental treatments including bevacizumab, thalidomide or vorinostat. In the first study, the combination of pemetrexed and cisplatin was tested with or without bevacizumab (MAPS) in chemotherapy naive patients [10]; in the second study patients who completed first-line chemotherapy received either thalidomide together with active supportive care or active supportive care alone (NVALT-5) [11]; in the third study patients were either treated with vorinostat or placebo (VANTAGE-014) [12]. With regard to overall survival (OS), the pooled analysis revealed that targeted therapies improved the OS in comparison to the control arm (HR = 0.95, 95% CI: 0.76–1.19; P = 0.68, Fig. 1A), even though this result lacks statistical significance. The analysis was performed using a random-effects model due to the absence of heterogeneity ($I^2 = 0\%$). When looking at progression free survival (PFS), the pooled analysis showed a statistically significant improvement related to the use of targeted therapies (HR = 0.75, 95% CI: 0.60–0.94; P = 0.01 Fig. 1B). The random-effects model was used for the analysis of the PFSs due to the presence of high heterogeneity ($I^2 = 72\%$) among the considered trials.

Data from the literature clearly indicated the lack of randomized clinical trials testing targeted treatments for mesothelioma. In fact only three RTCs studies met our search criteria. The anti-angiogenic (anti-VEGF) monoclonal antibody bevacizumab combined with standard cisplatin and pemetrexed treatment significantly improved PFS and OS [10]. Thalidomide, another anti-angiogenic and immunomodulating compound, induces apoptosis of new vasculatures as well as stimulates an immune response against cancer cells. When given to MPM patients as second line therapy, however, it failed to induce a measurable anti-tumour response [11]. Conversely, histone deacetylase inhibitor vorinostat on its own was able to improve PFS, while not OS, suggesting potential efficacy in combination regimens [12]. From our analysis, only 2 of the 3 targeted therapies, bevacizumab and vorinostat, showed statistical improvement of PFS of MPM patients. It is worth considering that targeted drugs could be more efficient when used in combination with other therapies, as the elicited cytostatic effect may not be “enough” to generate a measurable anti-tumour response in the single-agent setting. As our report suggests, there is a need for more RTCs studies testing targeted therapies, both as single therapy and in combination with other targeted and/or systemic drugs. The main drawback in mesothelioma clinical trials is the small number of patients enrolled, because of the intrinsic nature of the disease. In fact, MPM patients are relatively low in number because of the biology of the tumour and the fact that the disease is generally diagnosed in its late stages. However larger cohorts of patients enrolled in randomized trials would increase the reliability and scientific significance of the findings.

We declare no competing interest.

Sincerely,

Navid Sobhani, MSc

Giandomenico Roviello, MD

Silvia Paola Corona, MD, Ph.D

Anna Ianza, MSc

Fabrizio Zanconati, Professor of Medicine
 Daniele Generali, Professor of Medicine
 Department of Medical, Surgery & Health Sciences,
 University of Trieste, Piazza Ospitale 1
 34129 Trieste, Italy.

Table 1
 Characteristics of the analysed trials.

Study	Phase	Primary endpoint	Number of Patients Exp Arm	Number of Patients Control Arm	Line	Exp arm	Control arm	Jaded Score
MAPS [10]	III	Overall survival	223	225	I	pemetrexed plus cisplatin plus bevacizumab.	pemetrexed plus cisplatin	4
NVALT-5 [11]	III	Time to progression	111	110	Maintenance After first line	Thalidomide	Supportive care	5
VANTAGE-014 [12]	III	Overall survival/safety	329	332	II	vorinostat	Placebo	5

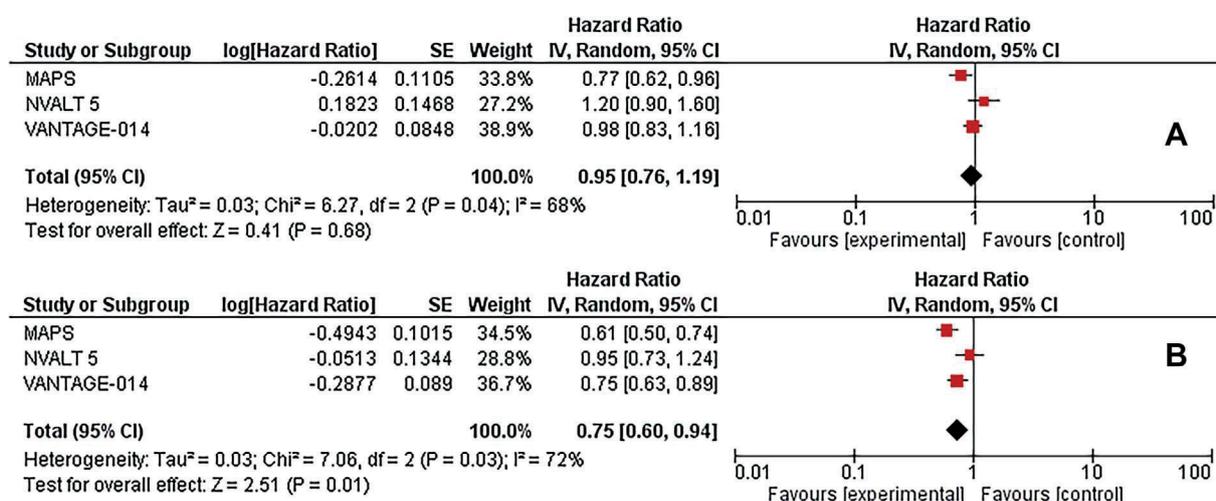


Fig. 1. (A) Forest plots of hazard ratios (HRs) for overall survival (OS) comparing new targeted therapies to the control arm. (B) Forest plots of hazard ratios (HRs) for progression free survival (PFS) comparing new targeted therapies to control arm.

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N. Sobhani*

Department of Medical, Surgery & Health Sciences, University of Trieste, Piazza Ospitale 1, 34129 Trieste, Italy
 E-mail address: n.sobhani.08@aberddeen.ac.uk

* Corresponding author.

G. Roviello
Medical Oncology Unit, Department of Oncology, San Donato Hospital, Via Nenni 20, 52100 Arezzo, Italy
Department of Medical, Surgery & Health Sciences, University of Trieste, Piazza Ospitale 1, 34129, Trieste, Italy

S.P. Corona
Department of Radiation Oncology, Peter MacCallum Cancer Center, Moorabbin Campus, 823-865 Centre Rd, Bentleigh East, VIC 3165, Australia
E-mail address: paola.corona@petermac.org

A. Ianza, F. Zanconati, D. Generali
Department of Medical, Surgery & Health Sciences, University of Trieste, Piazza Ospitale 1, 34129 Trieste, Italy
E-mail address: fabrizio.zanconati@asuits.sanita.fvg.it